AMENDMENTS TO THE FIGURES:

Please replace Figure 9 in the above-captioned application with the attached replacement Figure 9, labeled "Replacement Sheet," in compliance with 37 C.F.R. §1.84. A marked-up copy of the amended drawings is also attached, labeled "Annotated Marked-up Drawings," on which the amendments are indicated in red ink. Applicants submit that no new matter has been added to the drawing.

Attachments following the last page of this Amendment:

Replacement Sheet (1 page)

Annotated Marked-up Drawings Showing Changes (1 page)

REMARKS

A check for the fee for a five month extension of time accompanies this response. Any fees that may be due in connection with the filing this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Summary of Examiner Interview

Karen Potter, a registered Patent Agent, telephoned the Examiner Russell Negin on April 11, 2006 inquiring whether the Preliminary Amendments filed in the case had been made of record. In particular, Karen Potter discussed informalities in the Restriction Requirement mailed February 10, 2006 regarding consideration of Preliminary Amendments filed in the case. For example, in the Preliminary Amendment mailed July 11, 2005 several claims were cancelled, yet these claims were included within the restricted subject matter. The Examiner noted that he would review the Preliminary Amendments filed in the case and that if they impacted the Restriction Requirement he would draft and mail a supplementary Restriction Requirement. A supplemental Restriction Requirement was mailed.

Other issues

In the supplemental Restriction Requirement mailed April 20, 2006, the Examiner notes that Preliminary Amendments of July 11, 2005 and August 19, 2005 are made of record. Please confirm that the Preliminary Amendments filed April 08, 2004 and April 29, 2004 also have been made of record in this case.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement has been filed under separate cover on the same day as the instant election and amendment.

Amendments

IN THE SPECIFICATION

Amendments to the specification seek to correct minor typographical, spelling and formatting errors. For example, amendments to the paragraph at page 1 seek to correct reference to the corresponding application, which is the corresponding PCT application to the instant U.S. application and therefore is not a U.S. application. In addition, reference to the Attorney docket No. has been replaced with reference to the now available Serial No. Further, the filing date of U.S. Serial No. 10/658,355, which was filed the same day as the instant application, was amended to specify the actual filing date.

In addition, amendments to Table 5 at page 145 to page 147 of the instant application seek to correct the description of mutants at position 42 and position 91 listed in column 1 of Table 5, whereby the replacing Ala (A) amino acid was inadvertently omitted. Table 5 summarizes Alanine (A) mutants of IFNα-2b generated by Ala-scan. Basis for this amendment can be found in the SEQ ID NO identifiers for the respective mutants listed in column 2 of Table 5 and the Sequence Listing. For example, SEQ ID NO: 32 is the sequence identifier for the E41 mutant, and SEQ ID NO:32 depicts an IFN-α2b mutant containing a mutation of E41A. SEQ ID NO: 65 is the sequence identifier for the Q91 mutant, and SEQ ID NO:65 depicts an IFN-α2b mutant containing a mutation of Q91A. An additional amendment to Table 5 seeks to correct an inadvertent error in referencing of a SEQ ID NO by deleting the referenced SEQ ID NO for the Q101A mutant. SEQ ID NO:207 designates an interleukin-4 sequence, as is described at Page 5, line 19 of the Specification and depicted in the Sequence Listing. Amendments to Table 7 at page 148 to page 149 also seek to correct an inadvertent error in referencing of a SEQ ID NO. Basis for this amendment can be found in the Sequence Listing where SEQ ID NO: 89 designates an E58Q IFN-α2b mutant, while SEQ ID NO:90 designates an E58H IFN-α2b mutant, such as is depicted in column 1, row 20 of Table 7.

No new matter has been added to the specification.

IN THE FIGURES

In accordance with 37 C.F.R. §1.121(d), amendments to the drawing of Figure 9 (Fig. 9) of the above-referenced application is respectfully requested. Attached herewith is a replacement drawing of Fig. 9, labeled "Replacement Sheet," in compliance with 37 C.F.R. §1.84. A marked-up copy of the drawing, labeled "Annotated Marked-Up Drawings," also is enclosed herewith; the amendments to the Fig. 9 are indicated in red ink. Amendments to the Figures include amendments to Fig. 9 to correct the amino acid sequence of EPO depicted in Fig. 9. The sequence of EPO depicted in Fig. 9 inadvertently has two incorrect amino acids listed at positions 121 and 122 with respect to the mature EPO amino acid sequence. Fig. 9 is amended herein to correct these inadvertent errors by amending the sequence to replace the Asparagine (N) and Serine (S) residues at positions 121 and 122, respectively, with Proline residues at both positions, as depicted in the mature wild-type sequence of EPO listed in SEQ ID NO: 201 of the Sequence Listing. Basis for this amendment can be found within SEQ ID NO: 201 of the Sequence Listing as originally filed. SEQ ID NO: 201 is also described in the specification at page 6, lines 7-8, page 57, lines 11-12, and 82 lines 12-13 as erythropoietin

(EPO). As further support for the amendment, the amino acid Proline is listed as the wild-type amino acid for both positions 121 and 122 in Figure 12L and in claim 90 as originally filed. No new matter has been added to the Figures.

IN THE CLAIMS

Claims 1, 5-9, 16-19, 21-23, 40, 43-44, 46-74, 139-144, 279, 306-308, 315-316 and 332-343 are pending in this application. Claims 2-4, 10-15, 20, 24-39, 41-42, 45, 75-138, 145-278, 280-305, 309-314 and 317-331 are cancelled herein without prejudice or disclaimer. Applicant reserves the right to file divisional and continuation applications to any non-elected or cancelled subject matter. New claims 332-343 are added. No new matter is added. Non-elected subject matter is retained for possible rejoinder.

Claim 1, 5-9, 23, 46 and 279 are amended herein to conform the claims to the election requirements. For example, claim 1 is amended to recite that the modified cytokine is a modified interferon alpha cytokine. Basis for this amendment can be found in original claim 1 and in original claim 4, which has been canceled and incorporated into amended claim 1, and in the specification, such as for example, at page 5, lines 1-19. Hence, dependent claims 23 and 279 are amended herein to recite only those sequence identifiers that set forth modified interferon alpha molecules. Claims 8 and 9 are amended herein to consolidate the claimed subject matter by specifying that the duo-amino acid replacements are additional replacements to those set forth in claim 6. Basis for this amendment can be found in the specification, for example, at page 59, lines 22-31; and at page 65, lines 3-6. New claims 332-343 are added and find basis in the specification such as, for example, at page 5, lines 7-10; at page 5, lines 17-19; at page 5, line 24-27; at page 53, lines 16-18; at page 54, lines 17-20; at page 58, lines 13-20; at page 60, lines 1-3; at page 60, line 17 to page 61, line 2; at page 94, lines 23-24; at page 119, lines 27 to page 120, line 4; and at page 120, line 14 to page 121, line 4. No new matter is added.

Traverse of the Restriction Requirement

The requirement for restriction as set forth is traversed. While there are a number of grounds for traversing this requirement, cancellation of claims herein renders such grounds moot at this time. Applicant's silence regarding such issues is not to be construed as an acquiescence therewith. Traversal, set forth below, is on several grounds.

Applicant respectfully traverses the Requirement for Restriction as between Group I and Group V and as between Group I and Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI,

XVII, and XVIII. In addition, Applicant respectfully requests reconsideration of the restriction among the restricted polypeptides.

Election of Sequence and Election of Species

The Office Action has set forth a requirement for an election of a single polypeptide, whose sequence is set forth in any of SEQ ID NOS: 2-181, 233-1303. In addition, the Office has set forth a requirement for an election of species of a single mutant. Traverse is on two grounds. First, the requirement for election of a sequence and election of a species is inconsistent and duplicative; and second some of the molecules are encoded by the same gene or gene family, and hence, in accord with the PTO's own rules, should not be separated.

1) First, it is respectfully submitted that the requirement to elect a sequence and to elect a species are mutually exclusive. An election of species is an election for search purposes. Hence election of a single molecule is to guide the search. At the same time, the Action requires election of a single molecule belying the election of species. Since an election of species is a search tool, not a restriction requirement, one cannot effect both elections. For purposes of the response and amendments herein, the requirement is treated as an election of species. To be responsive, the same molecule is elected for both elections.

2) Second, notwithstanding the above traversal, it respectfully is submitted that the claimed polypeptides are modifications of members of the same family of proteins. Interferon α proteins are encoded by a related family of genes. All of the modified polypeptides as claimed are interferon α proteins. The claims recite mutations without reference to family member, since there are corresponding mutations across the gene family. Hence the claimed polypeptides include those that are encoded by the same gene, *i.e.* interferon-α-2b. The modified interferon-α-2b. are encoded by the same gene, and, thus, should be grouped together (see MPEP 803.04). For example, sequences to modified interferon alpha molecules set forth in any of SEQ ID NOS: 2-181, 978-988 or 1303 should be examined together. At the minimum, at least 10 of SEQ ID NOS: 2-181, 978-988 or 1303 should be searched.

Furthermore, the alpha interferon genes constitute a single family of related genes; in assessing patentability of one family member (*i.e.* an interferon α-2b), the corresponding family members (*i.e.* an interferon α-2a) must be searched to assess issues such as obviousness. Therefore all interferon-α modified polypeptides should be examined.

Restriction to a single molecule

Restrictions to single nucleotide or polypeptide molecules are discussed in §803.04 of the Manual of Patent Examining Procedure (MPEP). According to MPEP §803.04, claims drawn to nucleotide molecules encoding different proteins are deemed properly restrictable, but the Commissioner has decided *sua sponte* to partially waive this requirement for a reasonable number (usually, ten) of patentably distinct sequences. MPEP §803.04 states:

> Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. In addition to the specifically selected sequences, those sequences which are patentably indistinct from the selected sequences will also be examined.

Further, MPEP §803.04 states:

> Furthermore, nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together.

In this instance, the Examiner only is permitting examination of a single molecule, not the reasonable number, as set forth in MPEP §803.04. Thus, since the Commissioner has deemed that more than one molecule per case is permitted, at least 10 of SEQ ID NOS: 2-181, 978-988 or 1303 should be searched.

Furthermore, it is respectfully submitted that to the extent that the claims encompass polypeptides of the same protein, such polypeptides should be examined together. In this case, the molecules are modified cytokines of the same protein and are encoded by the same gene. As set forth in MPEP §803.04, sequences that encode the same protein should be examined together. There is no burden to search a single gene, and the encoded modified forms.

In this application, SEQ ID NOS: 2-181, 978-988 or 1303 set forth the sequences of modified IFNα-2b polypeptides. Accordingly, all modified IFNα-2b cytokines set forth in SEQ ID NOS: 2-181, 978-988 or 1303 should be examined in the same application, as each of these represent modified polypeptides of an IFNα-2b. Furthermore, as noted above, the interferon alpha proteins are encoded by a family of genes; a search for one member of the family necessarily will require a search for the corresponding family members. Therefore, even if the requirement to elect a single polypeptide is upheld, all family members should be included. Applicant should not be required to file a separate application to each and every mutant disclosed in this application, including separate applications to polypeptides with mutations corresponding to E41Q in each of alpha interferon alpha mutations. The Search will

necessarily include such mutations. Therefore, reconsideration of the requirement for restriction to one molecule per application respectfully is requested.

Claims 1, 5-9, 16-19, 21-23, 40, 43-44, 46-74, 139-144, 279, 306-308, 315-316 and 332-343 are linking claims

In addition, genus claims are linking claims. Each of claims 1, 5-9, 16-19, 21-23, 40, 43-44, 46-74, 139-144, 279, 306-308, 315-316 and 332-343 is generic to the elected species and molecule. Pursuant to MPEP §809, when claims linking more than one group are found, the Restriction Requirement must be conditioned on:

1) specifying the linking claims; and

2) examining the linking claims with the elected group. The linking claims must be examined with the elected group; if the linking claims are deemed allowable, then the restriction requirement must be withdrawn and all claims directed to nonelected subject matter that depends from or includes all the limitations of the linking claims must be rejoined Thus, claims 1, 5-9, 16-19, 21-23, 40, 43-44, 46-74, 139-144, 279, 306-308, 315-316 and 332-343 must be examined with the elected molecule or species. Upon a determination that any linking claim is allowable the restriction requirement as between that claim and all linked groups must be withdrawn.

Therefore, examination of all pending claims is respectfully requested.

Traverse of the requirement as between Group I and Group V

The Examiner requires election of the subject matter of Group I (original claims 1-24, 40-48, 139-144, 306-331) directed to a modified cytokine and of the subject matter of Group V (Claim 39) directed to a modified cytokine with two or more mutations. It respectfully is submitted that the requirement for restriction as between groups Group I and Group V is inconsistent, since identical subject matter is contained within the claims of each group. For example, claim 21 of Group I also is directed to a modified cytokine containing two or more mutations. Hence, claim 39 of Group V is canceled herein as it is duplicative of the subject matter of claim 21, which was properly included in the subject matter of Group I.

Furthermore, the subject matter claim 39 (or 21) and claims of group 1 are related as a subcombination/combination. For example, the elected molecule is an interferon α that has the mutation E41Q (or the corresponding mutation in the other family members based on structural homology). A molecule that further comprises a second mutation, is related to the first molecule as a combination/subcombination.

Inventions that are related as a combination and subcombination are distinct and restriction may be proper only if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability and (2) the subcombination has utility by itself or in other combinations. See MPEP 808.05(c). In this instance, if the subcombination, a molecule with a single mutation is patentable, a molecule with that mutation plus an additional mutation is necessarily patentable. Therefore, as between claims to a molecule with a single mutation and molecules that further contain additional mutations, restriction is not proper.

In addition, claims in group 1, are linking claims that link groups I and V (claim 39). Claim 1 and claim 39 are related as genus/species, since claim 1 encompasses claim 39. As noted above, genus claims linking species claims are one example of linking claims. See MPEP §809.03. Thus, claim 1 is a linking claim. Pursuant to MPEP §809, when claims linking more than one group are found, the Restriction Requirement must be conditioned on:

1) specifying the linking claims; and

2) examining the linking claims with the elected group. The linking claims must be examined with the elected group; if the linking claims are deemed allowable, then the restriction requirement must be withdrawn and all claims directed to nonelected subject matter that depends from or includes all the limitations of the linking claims must be rejoined. Therefore, Groups I and V are linked, and should be rejoined upon a determination that claim 1 or other linking claim in Group I is allowable.

Also, it is apparent that this requirement is improper, if one considers the outcome if patents issued based upon each of these two groups. If the claims are restricted into these two groups, Applicant ultimately could be granted two patents that expire on different days and/or are not required to be commonly owned. For example, if claim 39 in Group V issues before claim 1 in Group I, the issued patent will include a claim (*i.e.* claim 39) that is a species of claim 1. Claim 1, which could be pending in another divisional application, encompasses the species in claim 39. The Office, however, will be precluded from rejecting it based on obviousness-type double patenting over claim 39. The Examiner is reminded of the cautionary language in MPEP §806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Where restriction is required by the Office double patenting cannot be held, and thus, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP §804.01, which states:

> 35 U.S.C. §121 authorizes the Commissioner to restrict the claims in a patent application to a single invention when independent and distinct inventions are presented for examination. The third sentence of 35 U.S.C. §121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 U.S.C. §121 prohibition applies only where the Office has made a requirement for restriction. The prohibition does not apply where the divisional application was voluntarily filed by the applicant and not in response to an Office requirement for restriction. This apparent nullification of double patenting as a ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same invention in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

In this instance, if the restriction requirement as between Groups I and V is maintained, the Office is precluded from rejecting the claims for obviousness-type double patenting. Therefore, reconsideration of the requirement for restrictions as between these groups is respectfully requested.

Group I and Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, and XVIII

Applicant respectfully requests reconsideration of the Requirement for Restriction as between Groups I and Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, and XVIII. Claim 1 of Group I is directed to modified interferon alpha cytokines,. In addition, claim 43 of Group I is directed to a modified cytokine that is a structural homolog of IFNα-2b at positions corresponding to the 3-dimensionally structurally similar modified positions on IFNα-2b and claim 46 of Group I further specifies that the modified structural homologs of claim 43 are any of IFNα-2a, IFNα-c, IFNα-2c, IFNα-d, IFNα-5, IFNα-6, IFNα-4, IFNα-4b, IFNα-I, IFNα-J, IFNα-H, IFNα-F, IFNα-8, and IFNα-consensus cytokine. Additional claims in Group I are generic to one or more of claims in one or more of Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, and XVIII. As such, claims in Group I link one ore more of these groups.

Claims in each of Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, and XVIII are directed to a specific modified IFNα family of molecule containing amino acid replacements at specified positions corresponding to the 3-dimensionally structurally similar modified positions on IFNα-2b. For example, claim 49 and dependents thereof (Group VI) are directed to a modified IFNα-c containing structurally-related modified amino acids

compared to IFNα-2b; claim 51 and dependents thereof (Group VII) are directed to a modified IFNα-2c containing structurally-related modified amino acids compared to IFNα-2b; claim 53 and dependents thereof (Group VII) are directed to a modified IFNα-d containing structurally-related modified amino acids compared to IFNα-2b; claim 55 and dependents thereof (Group IX) are directed to a modified IFNα-5 containing structurally-related modified amino acids compared to IFNα-2b; claim 57 and dependents thereof (Group X) are directed to a modified IFNα-6 containing structurally-related modified amino acids compared to IFNα-2b; claim 59 and dependents thereof (Group XI) are directed to a modified IFNα-4 containing structurally-related modified amino acids compared to IFNα-2b; claim 61 and dependents thereof (Group XII) are directed to a modified IFNα-4b containing structurally-related modified amino acids compared to IFNα-2b; claim 63 and dependents thereof (Group XIII) are directed to a modified IFNα-I containing structurally-related modified amino acids compared to IFNα-2b; claim 65 and dependents thereof (Group XIV) are directed to a modified IFNα-J containing structurally-related modified amino acids compared to IFNα-2b; claim 67 and dependents thereof (Group XV) are directed to a modified IFNα-H containing structurally-related modified amino acids compared to IFNα-2b; claim 69 and dependents thereof (Group XVI) are directed to a modified IFNα-F containing structurally-related modified amino acids compared to IFNα-2b; claim 71 and dependents thereof (Group XVII) are directed to a modified IFNα-8 containing structurally-related modified amino acids compared to IFNα-2b; and claim 73 and dependents thereof (Group XVIII) are directed to a modified IFNα-consensus cytokine containing structurally-related modified amino acids compared to IFNα-2b.

Linking claims

Thus, for example, claims 1, 43, and 46 of Group I are directed to a genus of modified cytokines that are interferon alpha structural homologs of IFNα-2b, and each of claims 49 (Group VI), 51 (Group VII), 53 (Group VIII), 55 (Group IX), 57 (Group X), 59 (Group XI), 61 (Group XII), 63 (Group XIII), 65 (Group XIV), 67 (Group XV), 69 (Group XVI), 71 (Group XVII), 73 (Group XVIII), and their dependents are directed to species of a modified interferon alpha structural homolog. Therefore claims 1, 43 and 46 and each of claims 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, and 73 are related as genus/species. Genus claims linking species claims are one example of linking claims. See MPEP §809.03. Thus, each of claim 1, 43 and 46 as well as additional claims in Group I are linking claims with respect

to one or more of Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, and XVIII. If any claim in Group I that links any of Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, and XVIII is deemed allowable, the Restriction Requirement as between the linked groups must be withdrawn.

Also, it is apparent that this requirement is improper, if one considers the outcome if patents issued based upon each of these two groups. If the claims are restricted into these fourteen different groups, Applicant ultimately could be granted fourteen patents that expire on different days and/or are not required to be commonly owned. For example, if any of claims 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, and 73 in Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, or XVIII issues before claim 1, 43 or 46 in Group I, the issued patents will include claims that are species of claims 1, 43 or 46. Claims 1, 43 or 46, which could be pending in another divisional application, encompasses the species in any of claims 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, and 73. The Office, however, will be precluded from rejecting claims in Group 1 (i.e. claims 1, 43 or 46) based on obviousness-type double patenting over any of claims 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, and 73. The Examiner is reminded of the cautionary language in MPEP §806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Where restriction is required by the Office double patenting cannot be held, and thus, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP §804.01, which states:

> 35 U.S.C. §121 authorizes the Commissioner to restrict the claims in a patent application to a single invention when independent and distinct inventions are presented for examination. The third sentence of 35 U.S.C. §121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 U.S.C. §121 prohibition applies only where the Office has made a requirement for restriction. The prohibition does not apply where the divisional application was voluntarily filed by the applicant and not in response to an Office requirement for restriction. This apparent nullification of double patenting as a ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same invention in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

In this instance, if the restriction requirement as between Group I and each of Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, and XVIII is maintained, the Office is precluded from rejecting the claims for obviousness-type double patenting. Therefore, reconsideration of the requirement for restrictions as between these groups is respectfully requested.

Overlapping subject matter

Notwithstanding the above, the subject matter in Group I overlaps with subject matter in each of Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, and XVIII. As noted above, claims in each of Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, and XVIII are directed to a specific modified IFNα family of molecule containing amino acid replacements at specified positions that exhibit increased protease resistance. Claim 46 of group I recites that the modified interferon α polypeptides that are protease resistant are any of IFNα-2a, IFNα-c, IFNα-2c, IFNα-d, IFNα-5, IFNα-6, IFNα-4, IFNα-4b, IFNα-I, IFNα-J, IFNα-H, IFNα-F, IFNα-8, Hence claim 46 includes subject matter that is claimed in each of Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, and XVIII. As noted above, if the requirement for restriction is maintained as between Group I and any of Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, and XVIII, if claim 46 issues first, obviousness-type double patenting cannot be held as between such patent and any patent directed to any of Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, and XVIII. Therefore the restriction requirement as drafted among Groups I and Groups VI, VII, VII, IX, X, XI, XII, XII, XIV, XV, XVI, XVII, and XVIII is improper.

* * *

In view of the above, examination of the application on the merits and allowance are respectfully requested.

Respectfully submitted,

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Cytokine regions susceptible to protease attack identified by structural alignment with Lead mutants of IFN α-2b

IFN-α2b CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDF**GFPQEEFGNQFQK**AETIPVL**HEMIQQIFNLFSTKDSSAAWDE**TLLDKFYTELYQQLNDLEACVIQG

VGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNL**QESLRSKE**

Exemplary protein of the interferons/interleukin-10 family

IFN-β MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNF**DIPEEIKQLQQFQK**EDAALTI**YEMLQNIFAIFRQDSSSTGWNET**IVENLLANVYHQINHLKTVLEEK

LEKEDFTRGKLMSSLHLKRYYGRILHYLKAKEYSHCAWTIVRVEILRNFYFINRL**TGYLRN**

Exemplary protein of the short-chain cytokines family

EPO APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLN**ENITVPDTKVNFYAWKRMEV**GQQAVEVWQG**LALLSEAVLRGQALLVNSSQ**PWEPLQLHVDKAVSGLRSL

TTLLRALGAQKEAI~~SNS~~**DAASAAPLRTIT**ADTFRKLFRVYSNFLRGKLKLYTGEA**CRTGDR**

Exemplary protein of the long-chain cytokines family

G-CSF TPLGPASSLPQSFLLKCLEQVRKIQGDGAALQEKLVSECATYKLCHPEELVLLGHSLGI**PWAPLSSCPSQALQ**LAGCLSQL**HSGLFLYQGLLQALEGISPELG**PTLDTLQL

DVADFATTIWQQMEEL**GMAPALQPTQGAMPAFASAF**QRRAGGVLVASHLQSFLEVSY**RVLRHLAQP**

FIG. 9